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ORIGINAL CONTRIBUTIONS

Does Tea Affect Cardiovascular Disease? A Meta-Analysis

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This meta-analysis of tea consumption in relation to stroke, myocardial infarction, and all coronary heart disease is based on 10 cohort studies and seven case-control studies. The study-specific effect estimates for stroke and coronary heart disease were too heterogeneous to be summarized (homogeneity $p < 0.02$ for stroke, $p < 0.001$ for coronary heart disease). Only the relative risk estimates for myocardial infarction (seven studies) appeared reasonably homogeneous (homogeneity $p = 0.20$). The incidence rate of myocardial infarction is estimated to decrease by 11% with an increase in tea consumption of 3 cups per day (fixed-effects relative risk estimate = 0.89, 95% confidence interval: 0.79, 1.01) (1 cup = 237 ml). However, evidence of bias toward preferential publication of smaller studies that suggest protective effects urges caution in interpreting this result. The geographic region where the studies were conducted appeared to explain much of the heterogeneity among coronary heart disease, myocardial infarction, and probably stroke results. With increasing tea consumption, the risk increased for coronary heart disease in the United Kingdom and for stroke in Australia, whereas the risk decreased in other regions, particularly in continental Europe. *Am J Epidemiol* 2001;154:495–503.

cardiovascular diseases; cerebrovascular accident; coronary disease; meta-analysis; myocardial infarction; tea

Tea is the second most common drink in the world. Because of the high consumption of tea, even small effects in persons could have a large impact on public health. The polyphenolic flavonoids in tea are thought to have a protective effect on cardiovascular disease. Oxidized low density lipoproteins occur in atherosclerotic plaques in the vascular system and heart (1). Flavonoids have antioxidative properties that prevent oxidation of low density lipoproteins in vitro and, as recently shown, in vivo as well (2–6). High concentrations of autoantibodies against oxidized low density lipoproteins have been found in patients with atherosclerosis (7, 8). Nevertheless, the relevance of these laboratory findings for a hypothetically protective effect of tea on cardiovascular disease remains unknown. Therefore, the goal of the present study was to analyze the estimated effect of tea consumption on cardiovascular disease in all published epidemiologic studies.

MATERIALS AND METHODS

To search for observational studies of tea consumption in relation to cardiovascular disease, we conducted a literature search in MEDLINE for papers published from January 1, 1966, to October 14, 2000. The keywords for the search were tea, coffee, caffeine, or flavonoids together with one of the following outcomes: cardiovascular disease, coronary heart disease, stroke, myocardial infarction, ischemic heart disease, cerebrovascular disease, or cardiovascular risk. We included references listed in the recovered articles as well as in review articles. We examined all observational studies directly, because some studies did not report results for tea and cardiovascular disease as the main result and did not mention these results in the abstracts of the articles.

Four reports on three early case-control studies (9–11) were excluded because they did not include sufficient information to compute an estimate of relative risk or its standard error. (Throughout this paper, the term "relative risk" is used for incidence rate ratios estimated directly in cohort studies and by the exposure odds ratio in case-control studies.) In addition, two cross-sectional studies that measured serum levels and included undiagnosed cases (12, 13) were excluded. However, data from the latter cohort (13) were included as drawn from a separate publication (14). A report by Klatsky et al. (15) was replaced by a more recent analysis of the same cohort (16). In the report by Sato et al. (17), results from the prospective part of the study were used. We contacted the authors of 11 studies (14, 16–25) for information not included in their papers, such as variance estimates, numbers of subjects in categories of tea consumption, and typical tea cup sizes in specific locales. Nine authors responded to our request (see Acknowledgments).

The studies addressed a diversity of cardiovascular diseases (*International Classification of Diseases*, Ninth

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Revision, codes 390–459), which were combined in different ways (appendix table 1). We included the three outcome categories (myocardial infarction, stroke, and the broader category of coronary heart disease), which were examined in at least three studies. If a study provided more than one effect estimate for a single outcome category (14, 16), only one estimate was used.

The following paragraphs in this section pertain to statistical methods. The statistical analyses included 1) extracting or computing a common, comparable relative risk estimate from each study; 2) searching for evidence of publication bias; 3) analyzing interstudy variation; and 4) computing summary effect estimates as indicated. Evidence of publication bias and heterogeneity was taken to contraindicate reliance on overall summaries (23). In the presence of heterogeneity of effect, the main purpose of the meta-analysis became the identification of sources of interstudy variation.

We attempted to place the studies on a common footing by estimating the relative risk of a 3 cups per day increase in tea consumption (e.g., from no tea consumption to 3 cups per day) (1 cup = 237 ml). For studies reporting relative risk estimates in categories of tea consumption, we used inverse variance-weighted categorical regression to estimate linear exposure-response curves. These analyses were conducted on the incidence rate scale for cohort studies and on the logit scale for case-control studies. We used the covariance-corrected method of Greenland and Longnecker (26) for studies that provided the relative risk of tea consumption for more than two categories of tea consumption and provided the person-time per number of all subjects and cases per category of tea consumption (18, 20, 21, 25, 27–30). For other studies (14, 17, 19, 22, 23, 33, 34), we used the method described by Berlin et al. (31) and Greeland (32) or the relative risk for tea consumption as continuous (16, 24).

We assigned exposure values, in cups per day, to the tea consumption categories in the original studies as follows. For case-control studies, we used the tea consumption of the control groups. The various measures of tea consumption (cups, grams, milliliters) were transformed to a common measure of cups per day (1 cup = 8 ounces = 237 ml). When category medians (14, 20) or means (29, 33) were available, they were used. Category midranges were applied for the remaining closed-ended categories if they were no broader than 2 cups per day. If the highest, open-ended category included no more than 20 percent of the study subjects, we assigned that category a value equal to 1.2 times its lower boundary (18, 21–23, 25, 27). For the study by Stensvold et al. (19), more detailed data from an earlier report (35) on the same cohort were used to assign values to the tea consumption categories. Some of the closed-ended categories were wider than 2 cups per day in the studies by Rosenberg et al. (30), Jick et al. (34), and the Boston Collaborative Drug Surveillance Program (28). For these studies, we assigned category medians from the National Health and Nutrition Examination Survey I Epidemiologic Followup Study (36). In the Japanese study by Sato et al. (17), 41 percent of the subjects were in the highest, open-ended category. For this study, we used category midranges for the closed-ended categories. We used the factor 1.4 times the lower boundary of 7 cups per day for the highest, open-ended category instead of 1.2, because we expected the distribution to be skewed to the right, given the large proportion of people in the highest category.

The log-rank test of Begg and Mazumdar (37) was used for evidence of publication bias, with low p values suggesting the presence of bias. In addition, funnel graphs in which the study-specific effect estimates are displayed in relation to the reciprocals of their estimated variances were created (38). In the absence of publication bias, these graphs resemble a funnel with the estimates from the larger studies in the center, flanked symmetrically on either side by the less precise estimates.

To explore sources of heterogeneity among the studies, we performed stratified and meta-regression analyses (32, 39). The meta-regressions were fit using inverse variance-weighted, linear regression. The dependent variable was the log relative risk, and the independent variables were the study characteristics suspected of being sources of heterogeneity. After transformation back to the original ratio scale, the meta-regressions estimate the ratio of the average relative risk estimates reported by studies with one characteristic to the average estimates reported by studies with another characteristic. In this way, these models quantify the degree to which characteristics of the studies are associated with their results. The fit of the meta-regression models was checked by calculating the residual sum of squares (32).

We examined the following study characteristics in the stratified and meta-regression analyses: study design (cohort, case-control); mortality or morbidity data; geographic region (United States, United Kingdom, continental Europe, Asia, Australia); gender; adjustment for potential confounders by modeling, restriction, or stratification (sex and/or age, socioeconomic status, smoking, other nondietary risk factors for cardiovascular disease including alcohol, dietary factors); publication year (before or during 1980, 1981–1990, during or after 1991); age of subjects (<50 years, ≥50 years, all ages); participation rate (among the controls in case-control studies if separately reported); frequency of tea drinking in the study population (<50 percent, ≥50 percent drinking ≥1cup per day); and years of follow-up (cohort studies only). We were not able to investigate whether differences in dietary assessment methods accounted for heterogeneity because of the lack of description of the dietary assessment methods applied. Study characteristics were initially examined one by one, because of the lack of power to run them jointly due to the small number of studies. An attempt was made to examine jointly those characteristics that appeared in these analyses to be appreciably associated with the study-specific effect estimates.

To examine the effect of differences in the strength of tea in different regions quantitatively, we multiplied the assigned categorical dose by 0.5 and recalculated the summarized risk estimate for studies conducted in the United States on coronary heat disease or myocardial infarction. According to this calculation, we assume that the tea in the United States is half as strong as that in Europe. All analyses were conducted with Statistical Analysis System (SAS) software (40).

RESULTS

We identified and included 10 cohort studies and seven case-control studies (table 1, Appendix). Most studies suggested a decrease in the rate of cardiovascular disease outcomes with increasing tea consumption. Results from coronary heart disease or myocardial infarction are shown in figure 1. Two studies from the United Kingdom (14, 27) and two studies from the United States (21, 23) indicated an increased risk with increasing tea consumption, whereas the other studies indicated a decrease in risk. In table 1, the risk estimates were standardized for measuring the effects per 3 cups of tea per day. In the four studies showing an increased risk of coronary heart disease or myocardial infarction, the risk increased by 4–126 percent with each 3 cups/day (14, 21, 23, 27). In the other studies on coronary heart disease or myocardial infarction, the risk decreased between 1 and 75 percent per each 3 cups/day. For stroke, one of six studies showed an increased risk of 51 percent with each 3 cups/day (25), whereas the other studies indicated a decrease in risk of 26–66 percent with each increment of 3 cups per day.

The analyses of publication bias are summarized in figure 2. The small numbers of studies limit the interpretation, but the funnel graphs and the Begg-Mazumdar test both suggest the presence of publication bias for myocardial infarction and particularly for stroke. Specifically, it appears that smaller studies producing results inconsistent with the hypothesis of a preventive effect for myocardial infarction may have a very low probability of becoming published.

The results for cardiovascular disease categories were very heterogeneous ($p < 0.02$). The characteristic most strongly associated with the study-specific effect estimates was geographic region (table 2). Studies on coronary heart disease and myocardial infarction conducted in continental Europe reported much stronger inverse associations than did studies conducted elsewhere. On average, the relative risk estimates from continental Europe were about one third to one fourth of the magnitude of the estimates from the United States, with the exception of the two studies (14, 27) in the United Kingdom that reported a moderately strong positive association between tea intake and coronary heart disease. Neither the basic study design nor any other characteristic of the studies mentioned appeared to explain the heterogeneity of their results for coronary heart disease or myocardial infarction to any appreciable degree.

For studies on stroke, the follow-up time in cohort studies appeared to explain the heterogeneity among the studies. With each year of follow-up time the risk estimates decreased by 5 percent. In addition, the geographic region or study design explained heterogeneity. Because the one study from Australia showing a very different effect (increasing risk with increasing tea consumption) from the other studies from other geographic regions is also the only case-control study, it is not possible to determine if the geographic region or the study design explained heterogeneity.

The test for heterogeneity of the effect of tea on myocardial infarction showed no strong evidence of heterogeneity ($p = 0.20$) (table 3). The fixed-effects summary suggests a

TABLE 1. Overview and reanalysis of 17 observational epidemiologic studies of the effect of tea consumption on cardiovascular diseases

Study	Country	Outcome	RR* for 3 cups/day†,‡	95% CI*	Follow-up (years)	All subjects (no.)	Cases (no.)	Weights (1/SE²*)	% ≥ the following no. of cups/day§
Cohort study									
Hirvonen et al., 2000 (22)¶	Finland	Stroke	0.69	0.35, 1.36	6	26,415	736	75.77	17.7 ≥ 0.7 cup/day
Yochum et al., 1999 (24)	United States	CHD*	0.90	0.64, 1.26	10	34,492	438	303.14	25.0 ≥ 0.7 cup/day
		Stroke	0.73	0.38, 1.41	10	34,492	131	79.26	
Woodward and Tunstall-Pedoe, 1999 (14)	United Kingdom	CHD	2.26	1.10, 4.64	8	11,567	206	66.82	66.6 ≥ 1.3 cups/day
Hertog et al., 1997 (27)	United Kingdom	CHD	1.48	1.03, 2.12	14	1,900	131	265.79	85.8 ≥ 1.3 cups/day
Rimm et al., 1996 (23)	United States	CHD	1.47	0.95, 2.28	6	44,303	279	181.37	91.2 ≥ 2 cups/day
Keli et al., 1996 (33)	Netherlands	Stroke	0.34	0.17, 0.69	15	552	42	68.58	75.7 ≥ 1.4 cups/day
Hertog et al., 1993 (29)	Netherlands	CHD	0.29	0.11, 0.74	5	805	43	39.15	66.7 ≥ 1.1 cups/day
Klatsky et al., 1993 (16)	United States	CHD	0.95	0.80, 1.14	8	12,893	539	1,082.06	19.4 ≥ 1 cup/day
		MI*	0.91	0.74, 1.11		12,893	433	821.01	
		Stroke	0.84	0.64, 1.10		12,893	275	468.51	
Stensvold et al., 1992 (19)	Norway	CHD	0.25	0.12, 0.50	12	20,089	159	69.61	25.9 ≥ 1 cup/day
Sato et al., 1989 (17)	Japan	Stroke	0.68	0.56, 0.82	4	14,360	174	968.45	81.9 ≥ 1 cup/day
Case-control study									
Sesso et al., 1999 (20)	United States	MI	0.31	0.09, 1.02		680	340	23.76	32.0 ≥ 1 cup/day
Thrift et al., 1996 (25)	Australia	Stroke	1.51	0.89, 2.56		662	331	124.66	67.1 ≥ 1 cup/day
Gramenzi et al., 1990 (18)	italy	MI	0.29	0.10, 0.81		936	287	31.87	23.3 ≥ 1 cup/day
Rosenberg et al., 1988 (21)	United States	MI	1.04	0.66, 1.66		351	146	163.11	39.0 ≥ 1 cup/day
Rosenberg, et al., 1980 (30)	United States	MI	0.96	0.76, 1.20		1,423	472	668.96	40.9 ≥ 1 cup/day
Jick et al., 1973 (34)	United States	MI	0.91	0.63, 1.33		12,759	440	240.77	1.9 ≥ 5 cups/day
BCDSP,* 1972 (28)	United States	MI	0.81	0.58, 1.13		1,380	276	311.12	60.8 ≥ 1 cup/day

* RR, rate ratio; CI, confidence interval; SE², standard error squared; CHD, coronary heart disease; MI, myocardial infarction; BCDSP, Boston Collaborative Drug Surveillance Program, which also included subjects from Canada, New Zealand, and Israel.

† One cup = 237 ml.

‡ Rate ratio for drinking 3 cups/day vs. drinking no tea.

§ Percentage of subjects who drink at least the given number of cups per day (in case-control study only for control subjects).

¶ Numbers in parentheses, reference citations.

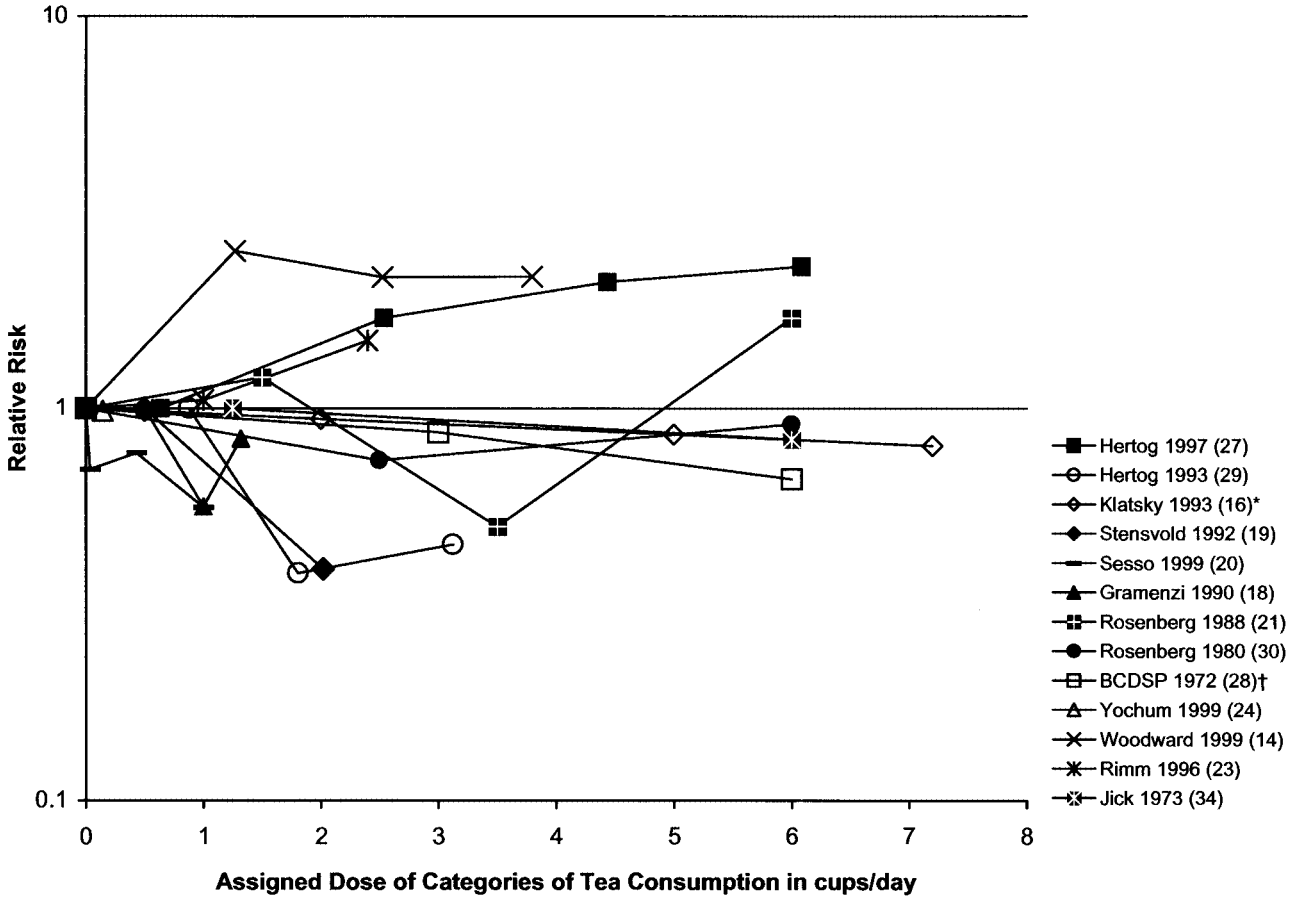

FIGURE 1. Relative risks of myocardial infarction or coronary heart disease with tea consumption as a categorical variable in observational epidemiologic studies (categorical values are shown as provided in the studies). One cup = 237 ml. *, the categorical risk estimates calculated from the continuous variable provided. †, BCDSP, Boston Collaborative Drug Surveillance Program, which also included subjects from Canada, New Zealand, and Israel.

decrease in incidence of myocardial infarction of 11 percent associated with an increment of 3 cups of tea per day (summary relative risk = 0.89, 95 percent confidence interval: 0.79, 1.01) (table 3). The evidence of publication bias, however, urges caution in interpreting this result.

Results stratified by region and study design are shown in table 3. For the broader outcome in which myocardial infarction is considered together with coronary heart disease, the results from the three studies in continental Europe are homogeneous ($p = 0.95$) and suggest that drinking an additional 3 cups of tea per day can reduce incidence by two thirds, an immense preventive effect. The eight studies conducted in the United States were less homogeneous ($p = 0.30$) with a beneficial effect, if any, being a reduction in incidence of only about 5 percent for each 3 cups/day. An increasing risk with increasing tea consumption was indicated for the two studies from the United Kingdom on coronary heart disease. These estimates also did not indicate strong evidence of heterogeneity ($p = 0.30$) with an increase in risk of 62 percent with each increment of 3 cups/day.

Additionally, we calculated the summarized risk estimate for studies conducted in the United States on coronary heart disease or myocardial infarction, assuming that tea in the United States is half as strong as that in Europe. In this case, the summarized risk estimate for studies conducted in the United States for coronary heart disease or myocardial infarction is 0.90 (95 percent confidence interval: 0.81, 1.01) with each increment of 3 cups/day rather than 0.95 (table 3).

The geographic stratified risk estimates of coronary heart disease alone were fairly similar to the risk estimates of coronary heart disease or myocardial infarction combined, although the results of the three studies from the United States were too heterogeneous ($p = 0.16$) to be summarized.

For myocardial infarction, the effect estimates from studies in the United States were reasonably homogeneous and suggested little or no effect. The fixed-effects summary from these six studies from the United States was almost identical to the estimate from the one study from Italy that was included (relative risk = 0.89 vs. relative risk = 0.91).

For stroke, the only case-control study conducted in Australia indicated a nonsignificant increased risk of 51 per-

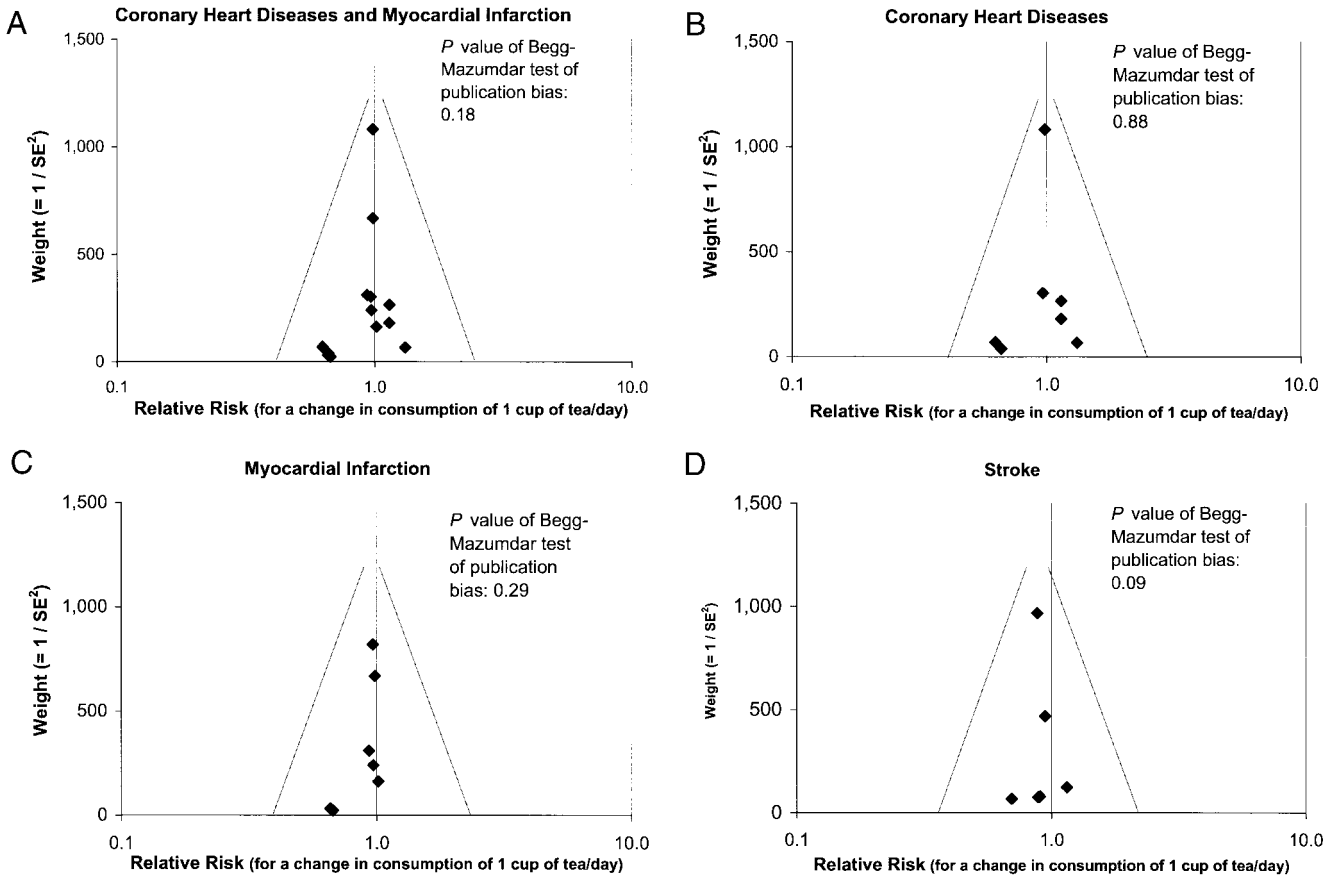

FIGURE 2. Funnel graphs of the relative risk for each cup of tea per day (beta coefficients) by the fixed-effects weights of a total of 17 observational epidemiologic studies of different cardiovascular diseases including myocardial infarction, coronary heart disease, or stroke. SE, standard error; 1 cup = 237 ml.

cent with each 3 cups/day (25). Cohort studies conducted in the United States, continental Europe, or Asia did not indicate strong evidence of heterogeneity ($p = 0.21$) with a significant reduction in stroke incidence of 12 percent per 3 cups of tea/day. The protective effect of tea on stroke increased in cohort studies by 5 percent with each year of follow-up (4–15 years).

DISCUSSION

The main purpose of this study was to examine the published literature on tea consumption and cardiovascular disease for evidence of publication bias and heterogeneity of effect and to summarize the effect estimates as indicated. Evidence of publication bias in the literature was apparent for myocardial infarction and particularly for stroke. The relative risk estimates for studies of myocardial infarction appeared homogeneous overall, although publication bias urges caution in interpreting this result. For coronary heart disease or myocardial infarction other than geographic region, no characteristic of the studies appeared to explain the heterogeneity or to be strongly associated with the study-specific results. Three studies from continental Europe were consistent in suggesting a strong preventive effect, whereas eight studies from the United States were consistent in suggesting little or no effect for coronary heart disease or myocardial infarction. Heterogeneity of risk estimates for stroke could be explained by length of follow-up together with study design and/or geographic region. Cohort studies not conducted in Australia indicated a decreased risk of stroke with increasing tea consumption. However, evidence of publication bias suggests extreme caution in interpretation of these data.

The small number of published studies for any specific cardiovascular disease outcome severely limited the ability to detect publication bias or heterogeneity. Tests of homogeneity are well known to have low power. Begg and Mazumdar (37) stated that their test for publication bias has moderate power with 25 studies and high power with 75 studies. It is impressive, therefore, that the p values from the tests for heterogeneity and publication bias were so low for stroke, despite the small number of studies in the published literature on the topic at hand. It would be of considerable interest to learn if epidemiologic researchers have examined results for tea and myocardial infarction and stroke and refrained from publishing them because they were not indicative of pronounced preventive effects. Only one of many possibilities is that publication bias on this question

TABLE 2. Estimated effect of the covariates' region and study design on the risk estimates of tea consumption on cardiovascular diseases in observational epidemiologic studies (results of a multiple linear meta-regression)

Covariates	Ratio of RR* for 3 cups/day†,‡	95% CI*	*p* value of model fit
MI* or CHD*			
Europe (without United Kingdom) vs. United States	0.27	0.14, 0.50	
United Kingdom vs. United States	1.73	0.97, 3.08	
CHD			
Europe (without United Kingdom) vs. United States	0.26	0.11, 0.62	
United Kingdom vs. United States	1.76	0.85, 3.63	0.96
MI			
Europe vs. United States	0.29	0.09, 0.92	0.52
Stroke			
Follow-up per each year	0.95	0.91, 0.98	
Australia vs. United States, Europe, Asia = case-control study vs. cohort study	1.51	0.73, 3.15	0.77

* RR, rate ratio; CI, confidence interval; MI, myocardial infarction; CHD, coronary heart disease.

† One cup = 237 ml.

‡ Estimated ratio comparing the relative risk (drinking 3 cups/day vs. drinking no tea) of a region or study design with the relative risk (drinking 3 cups/day vs. drinking no tea) of a reference region (United States) or reference study design (cohort study), computed as exp(3β).

has been stronger in Europe, where more people drink tea, than in the United States.

If studies with positive associations have not been published, as suggested by the tests of publication bias and funnel graphs, the central tendency would be closer to the null value. One cannot predict what the stratified and meta-regression analysis of study characteristics would show if a sizable number of unpublished studies were brought to light. The evidence of publication bias did not disprove the hypothesis of a protective effect, but it tempered the strengths of the conclusion regarding preventive potential.

The outcomes investigated in the studies had different definitions and were combined in more or less broad categories. If tea has different effects on different aspects of cardiovascular diseases, a combined estimate from various outcomes may minimize a tea effect. The results of the present meta-analysis suggest this possibility because the study results were less heterogeneous for myocardial infarction alone than for any less specific outcome. These results suggest that a more precise definition of the outcome might improve the homogeneity among studies and the precision in the effect estimate.

Case-control studies tend to have a higher potential for recall and selection bias. Nevertheless, we saw little or no difference in results between cohort studies and case-control studies for coronary heart disease or myocardial infarction. For stroke, it remains unclear if the differences were due to regional differences or differences in study design. The low number of studies limited the power to detect differences among the studies. If we expected the differences to be small, as possibly for differences in adjustment for confounding, we have limited ability to detect small differences in the meta-analysis.

For cohort studies on stroke, we found an increased protective effect with increasing length of follow-up between 4 and 15 years, which might indicate the importance of early prevention.

The findings from the United Kingdom and Australia of a positive association were unique. One possible explanation involves the polyphenolic antioxidant flavonoids hypothesized to be one mechanism by which tea might reduce cardiovascular disease incidence (1–7). In the United Kingdom, milk commonly is added to tea. Hertog et al. (27) reported that more than 99 percent of tea drinkers added milk and argued that this difference might explain why they did not find evidence of a protective effect of tea. Hasalam (41) showed that flavonoids are bound to protein. Further, indirect evidence suggested by Serafini et al. (42) showed that adding milk to tea abolished its in vivo plasma antioxidant potential. In contrast to these findings, however, Hollman et al. (43) and van het Hof et al. (44) did not find different flavonoid plasma concentrations in subjects given tea with or without milk. The hypothesis has been stated for the findings from the United Kingdom studies on coronary heart disease. This is also a possible explanation for the findings for stroke in Australia, a population that is strongly influenced by immigrants from the United Kingdom. In any event, the hypothesis of Hertog et al. (27) and Hasalam (41) might explain why an inverse association would not be seen in the United Kingdom and Australia, but that hypothesis would not explain why a positive association was seen. The amount of fat in the milk that is added to the tea would seem woefully insufficient to increase cardiovascular disease risk.

Sesso et al. (20) suggested that higher tea consumption might be a surrogate for a healthier lifestyle. Weak inverse associations of tea consumption with smoking, body mass index, and dietary risk factors have been reported (16, 19, 29). Residual confounding and lack of control for lifestyle factors might explain why some studies appear to suggest a protective effect of tea on cardiovascular disease. These problems may also explain regional differences. In the United Kingdom and in continental Europe, tea consumption is very common and therefore may not be restricted to people with healthier behaviors. Perhaps residual confounding and lack of control for lifestyle factors are especially pronounced in the United States, where fewer people drink tea and where weaker associations between tea and cardiovascular disease have been reported.

An important limitation of the studies was imprecision of the exposure measurement. Only the study from Japan investigated green tea. All other studies referred simply to

TABLE 3. Stratified effect estimates of tea consumption on cardiovascular diseases in observational epidemiologic studies

Outcome stratified for	No. of studies	Homogeneity *p* value	RR* for 3 cups/day†,‡	95% CI*
MI* or CHD*				
Europe (without United Kingdom)	5	<0.001		
Continental Europe and United States	11	<0.001		
United Kingdom	2	0.30	1.62	1.15, 2.30
Continental Europe	3	0.95	0.27	0.16, 0.44
United States	8	0.30	0.95	0.84, 1.08
CHD				
Europe (without United Kingdom)	4	<0.001		
Continental Europe and United States	5	0.22	0.77	0.54, 1.10
United Kingdom	2	0.30	1.62	1.15, 2.30
Continental Europe	2	0.79	0.26	0.15, 0.46
United States	3	0.16		
MI				
Continental Europe and United States	7	0.20	0.89	0.79, 1.01
Continental Europe (Italy)	1		0.29	0.10, 0.81
United States	6	0.53	0.91	0.80, 1.03
Stroke				
Australia or case-control study	1		1.51	0.89, 2.56
Europe, Asia, United States, or cohort study	5	0.21	0.88	0.82, 0.95

* RR, rate ratio; CI, confidence interval; MI, myocardial infarction; CHD, coronary heart disease.
† One cup = 237 ml.
‡ RR is the rate ratio for drinking 3 cups/day vs. drinking no tea.

tea. Some studies mention that the subjects were asked only about the frequency of tea consumption without any more detailed questions about the kind or preparation of tea. Tea comprises a heterogeneous group of beverages, including fermented black tea, half fermented oolongs, unfermented green tea, and sweetened or unsweetened ice tea, and it might even be understood to include fruit tea or herbal teas. It is to be expected that study subjects give a summary answer for any kind of tea if they are asked only about their tea consumption without more detailed questions. Different kinds of tea differ in the kind and quantity of substances and, even within the same kind of tea, differences exist. According to the analysis of Prior and Cao (45), the phenol content and antioxidant capacity of black, green, and herbal or berry teas can vary more than twofold. The mean total phenol content of black tea is 129.3 mg/g, of green tea, 71.7 mg/g, and of herbal/berry tea, 51.7 mg/g. In addition, the method of preparation affects the content of tea.

The information available was insufficient for us to address the kinds of tea, the methods of preparation, or the differences in tea strength. These factors might help to explain the regional differences we found, however. For instance, it might be expected that the kind of tea, method of preparation, and preference of tea strength differ among the regions and that there might be more similarity within a region than between regions. It is likely that the varying characteristics of tea have different effects on cardiovascular disease. If, for instance, Europeans tend to drink stronger tea than North Americans do, the effect per cup of tea could be higher in the European studies. We examined this hypothesis by recalculating the summarized risk estimate for coronary heart disease or myocardial infarction in the way that the tea in the United States is assumed to be only half as strong as that in Europe. In this case, the risk estimate for studies conducted in the United States decreased only from 0.95 to 0.90 with each 3 cups/day and is still very different from the summarized risk estimate in continental Europe of 0.27. It appears, therefore, that differences in tea strength may explain only a small fraction of the regional differences.

Because of the high consumption and distribution of tea worldwide, hypothetical health effects of tea are important public health issues. It appears worthwhile to address the regional differences in future research, while improving control for potential confounders and measurement of the many characteristics of tea and its preparation and consumption. Of greatest and most immediate importance would be for all investigators who have unpublished results on tea and cardiovascular disease to bring those results forward.

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APPENDIX

APPENDIX TABLE 1. Summary of adjustment of potential confounder and description of the outcome as used in 17 observational epidemiologic studies of the effect of tea consumption on cardiovascular diseases

Study	Outcome in meta-analysis	Disease outcome	Description of outcome (ICD-9* code)	Adjustment for potential confounder†
Hirvonen et al., 2000 (22)‡	Stroke	Fatal and nonfatal stroke incidence	430–431, 433–434	1, 2, 3, 11, 12, 15, 17, 21, 22, 23, 24
Yochum et al., 1999 (24)	CHD*	Mortality from CHD	410–414, 429.2	1, 2, 3, 6, 11, 12, 13, 15, 17, 23, 24, 25, 27, 28, 29, 31
	Stroke	Mortality from stroke	430–438	
Woodward and Tunstall-Pedoe, 1999 (14)	CHD	Mortality from CHD	ICD code not specified	1, 2, 5, 8, 11, 12, 13, 21, 22, 23, 24, 30, 37
Hertog et al., 1997 (27)	CHD	Mortality IHD*	ICD code not specified	1, 5, 11, 12, 15, 21, 22, 24, 25, 26, 30, 31, 32
Rimm et al., 1996 (23)	CHD	Mortality from CHD	ICD code not specified	1, 2, 3, 11, 12, 16, 17, 18, 22, 24, 27, 29, 31
Keli et al., 1996 (33)	Stroke	Fatal and nonfatal stroke incidence	430–438	1, 11, 21, 22, 24, 25, 33, 36
Hertog et al., 1993 (29)	CHD	Mortality from CHD	410–414	1, 11, 12, 13, 15, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 37
Klatsky et al., 1993 (16)	CHD	Mortality from CHD	ICD code not specified, chronic coronary	1, 2, 3, 4, 6, 11, 12, 24
	MI*	Mortality from acute MI	ICD code not specified	
	Stroke	Mortality from stroke	430–434	
Stensvold et al., 1992 (19)	CHD	Mortality from CHD	410–413, 414.0–414.1, 414.9, 798.1–798.2	1, 11, 21, 22
Sato et al., 1989 (17)	Stroke	Mortality from stroke	430–438	1, 2, 10, 11, 24, 34
Sesso et al., 1999 (20)	MI	Nonfatal MI	ICD code not specified, confirmed by evidence of creatine kinase	1, 2, 8, 11, 12, 13, 14, 15, 18, 19, 24, 25, 27
Thrift et al., 1996 (25)	Stroke	Nonfatal cerebral hemorrhage	ICD code not specified, based on discharge diagnosis	1, 2, 5, 7, 11, 12, 15, 22, 24
Gramenzi et al., 1990 (18)	MI	Nonfatal MI	ICD code not specified	1
Rosenberg et al., 1988 (21)	MI	Nonfatal MI	ICD code not specified, based on discharge diagnosis	1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 20, 22, 24, 37
Rosenberg et al., 1980 (30)	MI	Nonfatal MI	ICD code not specified, based on discharge diagnosis	
Jick et al., 1973 (34)	MI	Nonfatal MI	ICD code not specified, based on discharge diagnosis	
BCDSP,* 1972 (28)	MI	Nonfatal MI	ICD code not specified, based on discharge diagnosis	1, 2

* ICD-9, *International Classification of Diseases*, Ninth Revision; CHD, coronary heart disease; IHD, ischemic heart disease; MI, myocardial infarction; BCDSP, Boston Collaborative Drug Surveillance Program.

† 1, age; 2, gender; 3, education/profession; 4, race; 5, poverty index/social class; 6, marital status; 7, religion; 8, Framingham type A personality score/Bortner personality score; 9, year of interview; 10, geographic area; 11, smoking; 12, body mass index; 13, physical activity; 14, aspirin use; 15, history of myocardial infarction, coronary heart disease, hypertension; 16, other baseline disease; 17, diabetes; 18, family history of myocardial infarction or coronary heart disease; 19, family history of diabetes; 20, number of visits of physician in the previous year; 21, systolic and/or diastolic blood pressure; 22, serum cholesterol; 23, serum high density lipoprotein; 24, alcohol; 25, calories/energy; 26, fat; 27, saturated fat; 28, cholesterol; 29, dietary fiber/whole grain; 30, vitamin C; 31, vitamin E; 32, beta-carotene; 33, antioxidant vitamins; 34, salt intake; 35, calcium; 36, fish; 37, coffee.

‡ Numbers in parentheses, reference citation.